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REVIEW

The neurological and psychological phenotype of adult patients with early-treated phenylketonuria: A systematic review

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Abstract

Newborn screening for phenylketonuria (PKU) and early introduction of dietary therapy has been remarkably successful in preventing the severe neurological features of PKU, including mental retardation and epilepsy. However, concerns remain that long-term outcome is still suboptimal, particularly in adult patients who are no longer on strict phenylalanine-restricted diets. With our systematic literature review we aimed to describe the neurological phenotype of adults with early-treated phenylketonuria (ETPKU). The literature search covered the period from 1 January 1990 up to 16 April 2018, using the NLM MEDLINE controlled vocabulary. Of the 643 records initially identified, 83 were included in the analysis. The most commonly reported neurological signs were tremor and hyperreflexia. The overall quality of life (QoL) of ETPKU adults was good or comparable to control populations, and there was no evidence for a significant incidence of psychiatric disease or social difficulties. Neuroimaging revealed that brain abnormalities are present in ETPKU adults, but their clinical significance remains unclear. Generally, intelligence quotient (IQ) appears normal but specific deficits in neuropsychological and social functioning were reported in early-treated adults compared with healthy individuals. However, accurately defining the prevalence of these deficits is complicated by the lack of standardized neuropsychological tests. Future research should employ standardized neurological, neuropsychological, and neuroimaging protocols, and consider other techniques such as advanced imaging analyses and the recently validated PKU-specific QoL questionnaire, to precisely define the nature of the impairments within the adult ETPKU population and how these relate to metabolic control throughout life.

KEYWORDS

adult, early-treated, neurological, newborn screening, phenylketonuria

Abbreviations: ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; ETPKU, early-treated phenylketonuria; HRQoL, health-related quality of life; MeSH, medical subject headings; MRI, magnetic resonance imaging; Phe, Phenylalanine; PKU, phenylketonuria; QoL, quality of life; TNO-AZL, TNO Institute of Prevention and Health and the Leiden University Hospital.

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1 | INTRODUCTION

The natural history and devastating consequences of untreated phenylketonuria (PKU) are well described:

profound neurological damage with severe intellectual impairment and behavioral problems.¹ Seizures, behavioral problems, and movement disorders can be seen in untreated, late diagnosed patients, and in patients with long-term diet discontinuation.^{2–4} Fortunately, with early treatment and the consequent reduction of phenylalanine (Phe) levels in the blood and the brain, these effects are preventable.⁵ The introduction of universal newborn screening has transformed the outlook for people born with PKU, who should now be able to lead essentially normal lives.

Individuals with early-treated PKU (ETPKU) can obtain normal or near-normal intelligence quotient (IQ) if they maintain good metabolic control through dietary restriction until the age of 10, after which IQ appears to be fixed irrespective of Phe levels.⁶ Nevertheless, deficits in executive function, psychiatric symptoms, and abnormalities on neuroimaging have been reported in patients with ETPKU.^{7,8} However, it is unclear whether suboptimal outcomes are related to lack of metabolic control or to the burden of treatment. A recent retrospective cohort study suggests that neuropsychiatric symptoms are more prevalent in adults with well-managed PKU than in the general population, with many symptoms comparable with patients with diabetes mellitus, another chronic disorder that requires dietary restrictions.⁹ However, this study evaluated data from insurance claims databases, so precise information on treatment history was unavailable. It is not clear at this stage what proportion of adults with ETPKU suffer from these residual effects, or to what extent they affect their lives. Recent population-based surveys suggest that the majority of adults with ETPKU are, in fact, functioning well in society.^{10,11}

To develop evidence-based recommendations for the treatment of adults with ETPKU, any pathological features of this condition need to be described and the unmet medical need defined. Currently, the neurological phenotype of early-treated patients is not well characterized, and there are no cohort studies which systematically describe the neurological, neurocognitive, and neuroimaging features that can be seen, what proportion of people are affected, and what aspects of the phenotype relate to metabolic control. As detailed in the first European PKU guidelines, occasional case reports have described other problems such as Parkinsonism and cortical blindness in individual patients,^{12,13} but we do not know the prevalence of these potential complications, which might be expected to be seen primarily in older patients. Therefore, we undertook a review of the literature on neurological involvement in adult patients with ETPKU to better understand which medical issues have been reported in this population and to make recommendations on appropriate outcomes to be measured in future cohort studies in patients with ETPKU. Furthermore, we considered how neurological and neuropsychiatric involvement may affect quality of life (QoL) and social outcomes.

2 | METHODS

2.1 | Literature retrieval and screening strategy

A literature search of PubMed was initially performed using NLM MEDLINE controlled vocabulary (medical subject headings [MeSH] terms), with the MeSH term “Phenylketonuria” searched in conjunction with the MeSH term “Adult.” The search was restricted to exclude individual case reports, and include English language articles only from 1 January 1990 up to 16 April 2018 (the date of the search). Because indexing does not always occur immediately upon an article appearing in PubMed, a second search was performed with free-text terms on the titles and abstracts of articles dated 1 January 2015 to 16 April 2018. The free-text terms used were a combination of various synonyms of the initial MeSH terms “Phenylketonurias” and “Adult.” Individual case reports and non-English language articles were excluded. Finally, a third search was performed to account for articles from two relevant journals that were identified as not being indexed within PubMed, specifically *JIMD Rep* and *Mol Genet Metab Rep*. This search was the same as search 2, with the exception that it included articles only from these two journals, and the start date was set to 1 January 1990. The results from the three searches were combined and duplicates removed.

Retrieved papers were screened to select those reporting clinical data on behavioral, intelligence, mood, motor, neuropsychological, neuroimaging, neurological, psychiatric, QoL, or social outcomes among patients with a diagnosis of PKU (including patients with both mild PKU and classical PKU). Papers were then excluded if no relevant data from adults with ETPKU could be extracted (ie, data were generally excluded if they included a contribution from late-treated patients or children). Some rare but justifiable exceptions were allowed (eg, if relevant data were derived from a mixed cohort with a prevalence of adult ETPKU patients). Certain outcomes data were excluded if the selection of the population was intentionally biased (eg, IQ data were excluded for matched IQ studies). Data from patients who had discontinued dietary treatment before the age of 5 years were excluded. However, the level of lifetime dietary adherence (if reported) was not a criterion.

For the purpose of this review, the definition of “early treated” is that the patient was diagnosed by newborn screening and treated pre-symptomatically, as defined by the study in question, and the definition of “adult” is ≥ 16 years of age.

3 | RESULTS

Of the 643 articles retrieved from the initial search, 83 met criteria for inclusion in this review^{10,11,14–94} (Figure 1). Patients had been maintained on a Phe-restricted diet during

early childhood, although this did not necessarily equate to strict treatment; overall adherence to diet throughout their lifetime was not consistently reported and was variable between studies. Here, we discuss the key findings, with full tables of results presented in Supporting Information, Tables S1-S8.

3.1 | Neurological signs and symptoms

The literature search retrieved 13 articles that assessed neurological signs and symptoms in adult patients with ETPKU, of which the majority used routine clinical and neurological examinations (Table S1).

All studies reported abnormal neurological findings in the adult ETPKU population. The most commonly reported signs were tremor (postural and kinetic tremor), and hyperreflexia.

Where severity of tremor was reported, it was usually mild or moderate.^{32,58,59,70} Only two studies included a control group permitting direct comparison with healthy controls. One study with a larger sample size performed statistical evaluation but found no statistical difference between the incidence of tremor in patients (28%) and healthy controls (15%).⁵⁹ However, in the same study, fine motor skills were significantly impaired in patients compared with controls for measures of hand-wrist steadiness, dexterity and speed.⁵⁹ Although rare, more severe signs including ataxia, optic atrophy and spastic quadriplegia were reported in one study.⁵¹

Two studies assessed the impact of Phe levels on neurological signs.^{59,61} No significant difference was found in the level of Phe control between patients with and without tremor,⁵⁹ and no correlation between historical or current Phe levels and fine

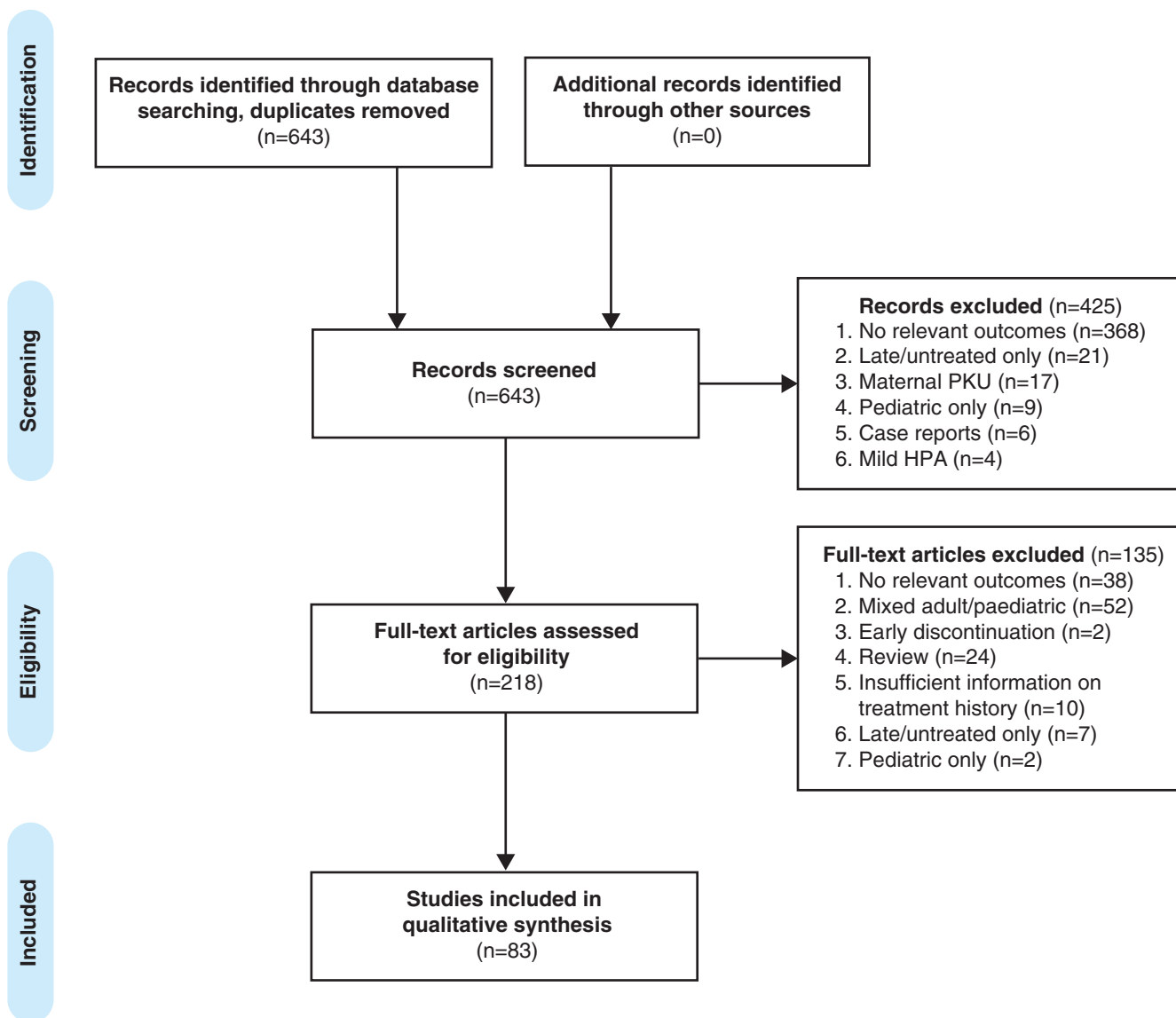


FIGURE 1 PRISMA flow diagram. The stages involved in literature review are outlined, along with the number of articles included/excluded, and the reasons for exclusion

motor skills.^{59,61} However, one study that compared patients who had never discontinued a Phe-restricted diet with those who had discontinued found that nearly a quarter of off-diet patients had neurological signs, relating primarily to changes in muscle tone and deep tendon reflexes. No signs were reported in the on-diet group, although it is important to note the small number of patients in this group.⁴¹

4 | IQ AND NEUROPSYCHOLOGICAL OUTCOMES

4.1 | Intelligence quotient

The literature search identified 47 articles that presented IQ data for adults with ETPKU. A range of standardized tests were used, each of which was generally calibrated such that the normal range of the general population was approximately 90 to 110 (Table S2).

Overall, while the IQ scores of adults with ETPKU were within the normal range, they were consistently lower when assessed in comparison to healthy subjects.^{32,55,59,83,92,94} Where assessed, dietary control and Phe levels at the time of testing did not have a significant impact on IQ.^{17,59,60} However, several studies correlated adult IQ with historical dietary compliance and Phe levels, particularly in early childhood and adolescence.^{58,60,74,83} IQ in patients and healthy subjects appears to remain constant once adulthood is reached, regardless of Phe levels.⁸³

4.2 | Neuropsychological, executive function, and attentional outcomes

The literature review retrieved 30 articles reporting on neuropsychological, executive function, and attention findings in adults with ETPKU (Table S3). Overall, 44 different testing methods were used across the studies (Table S4), assessing outcomes including working memory, sustained attention, attentional control, and response inhibition.

A number of well-controlled studies reported statistically significant deficits in patients compared with healthy control groups or normative populations across a range of neuropsychological and executive functions, including sustained and selective attention,^{17,22,27} working memory,^{22,27,38} response inhibition,⁴⁶ and letter fluency.²⁷ Two studies that performed extensive analyses on the same cohort of patients reported impairments in patients with ETPKU vs healthy controls, in the higher order executive functions, visuo-spatial attention and visuo-motor coordination, with significant variability across patients.^{92,94} Additionally, a recent study reported that compared with a control group, patients with ETPKU showed deficits in complex language tasks and were slower

and less accurate in tasks requiring planning and strategic abilities.⁸⁹ However, two studies that assessed executive function using the Behavior Rating Inventory of Executive Function questionnaire reported only slightly elevated scores compared with normative mean scores, which were not considered clinically significant.^{25,46}

The literature provides evidence for a significant link between the incidence of neuropsychological deficits and elevated blood Phe levels. Where analyzed, patients who had maintained good dietary control performed significantly better than patients with poor dietary compliance, on measures of executive functions including working memory, attentional control, and response inhibition.^{17,27,29} Performance on focused attention and aspects of memory was also shown to correlate with concurrent or recent Phe levels during adulthood.^{22,27} By contrast, working memory was significantly improved by lower Phe levels during childhood in adult patients adhering to a controlled diet, but showed conflicting results for off-diet patients.^{28,29} A significant association was reported between Phe levels during childhood and adolescence with executive functioning and executive motor control^{90,91} and with information processing and sustained attention performance in adulthood, but no change in performance was observed after 5 years of follow-up.⁸³

There is contradicting evidence on the effect of Phe levels, with one study reporting significant deficits in sustained attention during a high Phe condition,⁷⁹ while no such impact was reported on response inhibition⁷⁸ or on cognitive flexibility and working memory.⁸⁷

The association of Phe levels with adult cognition may depend on the age at which metabolic control was measured and on the particular cognitive domain examined. A recent study showed that performance on verbal memory and learning, visuospatial coordination and sustained attention were better predicted by recent Phe levels than control during childhood, whereas performances on visuospatial processing and complex executive functions showed a stable association with metabolic control across different ages.⁹⁴ Interestingly, a positive correlation has been found between striatal dopamine D_{2/3}R receptor availability, with impulsivity and error rate in a cognitive flexibility task, while there was no correlation with working memory or inhibitory control. These findings suggest that dopamine deficiency may impact the crucial role of the prefrontal cortex and striatum in executive functioning in adult patients with ETPKU.⁸⁷

5 | PSYCHIATRIC, MOOD, AND BEHAVIORAL OUTCOMES

The literature search retrieved 15 articles reporting on psychiatric, mood, and behavioral outcomes in adult patients

with ETPKU (Table S5). These studies reported on a range of psychiatric symptoms, often using standardized testing methods that allow comparisons with normative data.

Increased incidence of psychiatric symptoms in adult patients with ETPKU was reported in the literature, but not consistently between studies, and there was no evidence for an increased incidence of psychiatric diagnoses. One study reported a significantly higher incidence of several psychiatric symptoms among patients with PKU compared with a normative population, particularly in measures of psychoticism, paranoid ideation, obsessive-compulsive behavior, and depression.¹⁸ However, other studies found no significant difference between patients and control groups in the incidence of psychiatric disorders,⁶⁰ or measures of anxiety and depression.^{28,29} One study did find that patients with PKU experienced only internalizing disturbances (emotional problems such as depression and anxiety), while healthy controls exhibited both internalizing and externalizing disturbances (interpersonal problems such as antisocial behavior) equally.⁶⁰ Regarding sleep behavior, one study reported that adult patients with ETPKU presented more sleep disorders, reduced sleep quality, increased latency to fall asleep, and more daytime sleepiness compared with first degree relatives.⁸⁸

Average Phe levels have been reported to be significantly correlated with scores for psychoticism and psychiatric symptom intensity,¹⁸ while better Phe control during childhood was associated with better mood during adulthood.³⁰ Similarly, depression and anxiety scores were positively correlated with the age at diet initiation and childhood Phe levels, respectively.^{22,90} Equally, in other studies, psychiatric disturbance, anxiety, and depression were neither associated with current dietary status, nor with concurrent or historical Phe levels.^{28,60} Interestingly, one study found that patients with good dietary control during childhood reported a higher incidence of psychiatric disorders than those with poor dietary control, which the authors suggest may be attributed to the psychological stress incurred by adherence to a strict diet.⁴⁹ Similarly, another study found that a restrictive and controlling parenting style was a risk factor for the development of psychiatric symptoms,⁶⁰ although the relationship between parenting style and dietary adherence was not assessed.

6 | QUALITY OF LIFE

The literature search retrieved 11 articles reporting on QoL in adult patients with ETPKU. Several different questionnaires were used to assess QoL, however, only one article included a validated PKU-specific assessment¹⁹ (Table S6).

Several studies used standardized QoL tests, which reported good QoL in patients, comparable with that of healthy controls.^{21,26,30,54,76} However, specific QoL domains may be affected in adults with PKU, despite normal scores

overall. For example, patients scored significantly lower than controls only on the cognitive functioning domain of the TNO-AZL Adult QoL questionnaire.³¹ Furthermore, compared with the US general population, adult patients with PKU scored consistently worse in mental domains of the short form-36 questionnaire, while they achieved better scores on the physical domains.¹⁹ Elsewhere, the difference in physical and mental domain scores between patients and healthy controls was nonsignificant.^{28,29} Additionally, one study reported significantly lower QoL in male vs female patients, and in patients with lower educational level, despite a normal QoL score in the overall population.²⁶

Bosch et al evaluated health-related QoL (HRQoL) in mild-to-moderate and classical PKU patients (determined by Phe range at diagnosis), using a validated PKU-specific questionnaire designed to assess the impact of PKU on a patient's life. Using this questionnaire, patients with mild-to-moderate PKU tended to report a lower emotional, practical, social, and financial impact of PKU compared with patients with classical PKU.¹⁹ However, the impact of dietary management on QoL was comparable between patients with classical and mild PKU, possibly reflecting dietary relaxation during adulthood.¹⁹ In another study, patients on a restricted diet reported higher scores of general life-satisfaction than both an off-diet patient group and a reference sample.¹⁰ Moreover, some data suggest that returning to a strict diet after discontinuation for at least 3 months can significantly improve the subjective well-being of patients, according to evaluation with the Psychological General Well-Being Index.¹⁶

7 | SOCIAL OUTCOMES

Overall, the literature search identified 15 articles that reported on social outcomes in adult patients with ETPKU, variously assessed by standardized questionnaires and standard clinical interviews (Table S7).

Several studies reported comparable sociodemographic outcomes between patients and control populations, including comparisons with healthy siblings, in terms of employment, marital status, having children, education, and professional occupation.^{10,11,20,21,41} Additionally, no statistically significant difference was reported between patients and controls in the achievement of autonomy, psychosexual, and social developmental milestones.^{20,21}

When compared with patients with galactosemia, patients with PKU scored significantly better on psychosexual and social development, and were more frequently cohabiting/married and in employment,²⁰ suggesting that the outcomes of dietary treatment of PKU are better than those seen in galactosemia.

Two studies that provided comparative German census data did report differences in educational attainment between subjects with PKU and the general population. In the first study, patients with PKU, 96% of whom were on a restricted diet, achieved lower levels of academic achievement, specifically for graduation at senior high school level, compared with the general population.⁵⁴ The second study found that educational attainment was only lower in patients with PKU whose treatment was interrupted (for at least 4 years starting at the age of 7-14 years), while patients who had been continuously treated until the end of adolescence demonstrated comparable education status to the census population.¹⁰ Nevertheless, income was comparable between patients with PKU and the census population, regardless of therapy interruption.^{10,54}

Although evidence for the relationship between Phe levels and social outcomes is limited, some studies indicated that social factors in adult life are related to metabolic control during childhood,^{11,54} while one study found that social skills are not associated with concurrent Phe level.³⁸ There is also evidence to suggest that the demands of maintaining a low Phe diet itself may restrict a patient's lifestyle and social interactions.³⁴

8 | NEUROIMAGING

The literature review retrieved 35 publications reporting magnetic resonance imaging (MRI) findings in adult patients with ETPKU (Table S8). Most articles assessed white matter abnormalities using T2-weighted imaging.

In patients with ETPKU, overt atrophy is rare and conventional MRI typically discloses increased signal on T2-weighted images within periventricular white matter regions,^{32,63,75} brain stem, and cerebellum.⁶³

Other MRI techniques have also been used to report differences between PKU patients and healthy subjects. Diffusion-weighted imaging (DWI) provides evidence for significantly reduced apparent diffusion coefficient (ADC) in patients, demonstrating impaired water diffusion,^{32,48,80} which may indicate higher cell-packing density compared with controls.³³ Additionally, analysis of T2-relaxation reported markedly longer values in patients, indicating increased water content relative to controls,³² although this may be specific to patients with poor dietary control.³³ Brain volume may also be affected in patients with PKU, particularly with reductions of the cerebrum, pons, hippocampus, and corpus callosum regions compared with controls.⁵⁸

The results provide contradicting evidence for a relationship between dietary adherence and the severity of brain abnormalities. In one study, patients who had never discontinued a restricted diet tended to exhibit less severe white matter abnormalities than those who had discontinued or had a history of poor dietary control.⁷⁵ However, another study reported abnormalities despite the fact that all patients had

adhered to dietary treatment since birth.⁴⁸ Additionally, the severity of brain abnormalities were generally associated with historical Phe levels,^{30,50,55} while there appeared to be no relationship with Phe concentration at the time of MRI evaluation.⁵¹ Furthermore, there was no significant correlations between the volumes of different brain structures and current or historical Phe levels.⁵⁸

MR spectroscopy studies have repeatedly detected abnormal concentrations of brain Phe^{45,84} that may be specifically associated with white matter abnormalities.^{41,84} Interestingly, one study reported that milder white matter abnormalities were associated with lower brain Phe levels, but not blood Phe levels.⁴¹ Furthermore, a significant negative correlation between brain Phe levels and ADC was found to be specific to the corpus callosum.⁸⁰ Recently, two-dimensional shift correlated spectroscopy has been applied for the unambiguous quantification of cerebral metabolites, Phe and tyrosine, that present spectral overlap via conventional spectroscopy. With this technique, brain concentrations of these metabolites were significantly associated with some indices of neuropsychological functioning (eg, auditory memory and executive functioning).⁸¹

9 | CONCLUSIONS

The introduction of newborn screening means that people born with PKU can be expected to lead essentially normal lives. While patients who have been treated since birth may suffer some residual morbidity, the extent to which this affects the adult population is poorly characterized. This article represents the first systematic review to report on a strictly adult population of patients with ETPKU.

9.1 | Neurological

To date, there is little evidence for clinically relevant neurological morbidity in this early and continuously treated population of adults with PKU. It seems unlikely that the minor neurological signs and symptoms that have been described would have a negative effect on patients' everyday lives. Nevertheless, to confirm any relationship between Phe levels and neurological signs and symptoms, future studies should consistently test neurological functioning alongside Phe levels for every patient. Furthermore, there should be an effort to understand the temporal association of Phe levels with outcomes; for example, whether there are periods of life when the brain is particularly vulnerable to the effects of high Phe levels, and whether fluctuating Phe levels have different effects to stable Phe levels.

9.2 | IQ and neuropsychological outcomes

Although, on average, IQ in ETPKU adults appears to be within the normal range, significant deficits were reported in a number of neuropsychological, executive functions, speed, and attentional outcomes. An accurate summary of the neuropsychological deficits seen in this early treated population was made difficult by the wide range of different assessments used and the limited population studied: a survey into adult PKU management found that only 26% of healthcare providers perform routine neurocognitive tests in all of their adult patients.⁹⁵ However, the choice over the best neuropsychological test to use may be difficult to make in routine clinical practice. An easily administered test, such as BRIEF, may be well accepted by patients, but may not be sensitive enough to detect the subtle deficits reported in patients with ETPKU, nor to detect any new information after a short follow-up period. Conversely, a more sophisticated test may provide improved sensitivity, but would be more difficult to administer and be less likely to be accepted by patients, resulting in limited value for clinical purposes. To precisely define the neuropsychological phenotype of adult patients with PKU, a consensus needs to be reached on an appropriate testing battery and the timing for administration.

9.3 | Psychiatric, mood, behavioral, and social outcomes

Issues with mood and social functioning were found more often than deficits of executive function in ETPKU adults^{38,79}; however, there is no evidence that adults with ETPKU have a significantly higher incidence of psychiatric, mood, behavioral, or social problems than the general population. Nevertheless, the incidence of certain mood and behavioral outcomes, especially anxiety, could be further explored in future studies. Furthermore, evidence for the impact of dietary restriction on these outcomes was inconsistent. Further research into the psychiatric and social outcomes of adults with PKU should focus on understanding if there is a direct correlation between Phe levels and psychosocial difficulties, or whether such difficulties that patients experience are caused by the demands of maintaining a restricted diet.

9.4 | Quality of life

Assessing the impact of ETPKU on QoL are limited by the fact that all but one of the articles retrieved from the literature used generic HRQoL assessments, which may not be sensitive enough to detect any specific problems related to PKU. Future research should utilize the recently developed PKU-QoL questionnaire that is specifically designed to assess the impact of PKU on all aspects of a patient's life. This includes evaluating the social and emotional impact of

PKU, as well as the impact of adhering to dietary restrictions and supplements.⁹⁶

9.5 | Neuroimaging

The pathogenesis of white matter abnormalities in PKU is not yet fully understood, therefore, the mechanism that links brain white matter abnormalities to possible cognitive impairment is difficult to unravel. Conventional brain MRI (FLAIR/T2-weighted imaging and DWI) represents a powerful, readily available, noninvasive tool for detecting brain changes in adult patients with ETPKU. Although routine MRI data currently have limited use in informing treatment decisions, future research may use regular examinations to monitor white matter changes in people with PKU as they age. Furthermore, a recent morphometric MRI study in a mixed population of adults and children showed gray matter volume reductions in the parietal and occipital cortex of patients with ETPKU.⁹⁷ This indicates that brain MRI changes in patients with ETPKU are not only confined to the white matter, highlighting the importance of performing brain MRI to better understand the disease. Advanced MRI quantitative techniques, which have already provided valuable pathogenic clues about brain involvement in ETPKU, are promising tools in the search for biomarkers, not only for investigating the efficacy of new treatments in a research setting but also, hopefully, in tailoring individual treatment to prevent irreversible brain injury.

10 | SUMMARY AND CONCLUDING REMARKS

This review of the current literature, excluding case reports, has found studies which show minor neurological findings; white matter changes on MRI; subtle but significant deficits in neuropsychological functions; an increased, but nonsignificant, incidence of psychiatric symptoms and possible social difficulties in selected populations of adults with ETPKU. Overall, however, these individuals have a good QoL and social and educational achievements similar to those of the general population. The fact that individuals with PKU are now leading normal lives is testimony to the success of newborn screening and the early institution of dietary therapy.

It is likely that some patients do have significant impairments that impact on their everyday function and it is not unreasonable for patients, physicians, and parents to worry that they, their patient or their child will be at risk. However, the current evidence does not indicate that there are long-term PKU-related health problems that are serious and irreversible. A better understanding of the impact of Phe levels on the precise range and frequency of problems seen in

adults with PKU will help to further develop the evidence-based approach to treatment guidelines, and make sure that patients have the best chances of realizing the full benefits of treatment while minimizing any adverse effects of overly strict management.

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CONFLICTS OF INTEREST

A.P.B. has received honoraria for presentations and board meetings from Amicus Therapeutics, Biomarin, Nutricia, Sanofi Genzyme. R.H.L. has received honoraria and travel support from Nutricia, Biomarin and Nestle HealthScience. R.M. has received honoraria from Merck-Serono SA and Biomarin. F.J.v.S was/is a member of Scientific Advisory Boards for Phenylketonuria (Merck-Serono SA, Arla Foods, Biomarin, APR, Nutricia, Nestle-Codexis Alliance, Moderna), has received grants from Nutricia, Codexis, Merck-Serono SA, and Biomarin, and honoraria from Merck-Serono SA, Biomarin, Vitaflo International, Nutricia/Danone, and Excemed. A.B. was/is a member of Scientific Advisory Boards for Phenylketonuria (Merck-Serono SA, Biomarin, Nutricia), has received honoraria from Merck-Serono SA, Biomarin, Nutricia/Danone. C.C. and A.C. declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

A.P.B., R.H.L., R.M., C.C., A.C., and A.B. were involved in planning and conducting the literature review and in writing the manuscript. F.J.v.S critically reviewed the manuscript. All authors reviewed and approved the final manuscript. A.P.B. serves as guarantor for the article and accepts full responsibility for the work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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